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(54) Title: CRYSTALLINE AND OTHER FORMS OF 4-AMINO-5-FLUORO-3-[6-(4-METHYLPIPERAZIN-1-YL)-1H-BENZIMIDAZOL-2-YL]-1H-QUINOLIN-2-ONE LACTIC ACID SALTS

(57) Abstract: The present invention relates to non-hydrate crystalline forms of 4-amino- 5-fluoro-3 -[6-(4-methylpiperazin- 1 -yl)- 1 H-benzimidazol-2-yl] - 1 H-quinolin-2-one lactic acid salts, solid pharmaceutical formulations containing the same and methods of use. The present invention also relates to crystalline hydrates of 4-arnino-5-fiuoro-3-[6-(4- methylpiperazin-l-yl)-lH-benzimidazol-2-yl]-lH-quinolin-2-one lactic acid salts, pharmaceutical formulations containing the same and methods of use related thereto. The present invention further relates to crystalline solvates of 4-amino-5-fluoro-3-[6-(4- methylpiperazin-l-yl)-lH-benzimidazol-2-yl]-lH-quinolin-2-one lactic acid salts.

CRYSTALLINE AND OTHER FORMS OF 4-AMINO-5-FLUORO-3-[6-(4-METHYLPIPERAZIN-1-YL)-1H-BENZIMIDAZOL-2-YL]-1H-QUINOLIN-2-ONE LACTIC ACID SALTS

FIELD OF THE INVENTION

The present invention relates to non-hydrate crystalline forms of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one lactic acid salts, pharmaceutical formulations containing the same and methods of use related thereto. The present invention also relates to crystalline hydrates of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one lactic acid salts, pharmaceutical formulations containing the same and methods of use related thereto. The present invention further relates to crystalline solvates of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one lactic acid salts. The present invention also relates to amorphous and mesomorphic forms of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one lactic acid salts.

BACKGROUND OF THE INVENTION

Capillaries reach into almost all tissues of the human body and supply tissues with oxygen and nutrients as well as removing waste products. Under typical conditions, the endothelial cells lining the capillaries do not divide, and capillaries, therefore, do not normally increase in number or size in a human adult. Under certain normal conditions, however, such as when a tissue is damaged, or during certain parts of the menstrual cycle, the capillaries begin to proliferate rapidly. This process of forming new capillaries from pre-existing blood vessels is known as angiogenesis or neovascularization. See Folkman, J. Scientific American 275, 150-154 (1996). Angiogenesis during wound healing is an example of pathophysiological neovascularization during adult life. During wound healing, the additional capillaries provide a supply of oxygen and nutrients, promote granulation tissue, and aid in waste removal. After termination of the healing process, the capillaries normally regress. Lymboussaki, A. "Vascular Endothelial Growth Factors and their Receptors in Embryos, Adults, and in Tumors" Academic Dissertation, University of Helsinki,

Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, (1999).

Angiogenesis also plays an important role in the growth of cancer cells. It is known that once a nest of cancer cells reaches a certain size, roughly 1 to 2 mm in diameter, the cancer cells must develop a blood supply in order for the tumor to grow larger as diffusion will not be sufficient to supply the cancer cells with enough oxygen and nutrients. Thus, inhibition of angiogenesis is expected to halt the growth of cancer cells.

Receptor tyrosine kinases (RTKs) are transmembrane polypeptides that regulate developmental cell growth and differentiation, remodeling and regeneration of adult tissues. Mustonen, T. *et al.*, J. Cell Biology 129, 895-898 (1995); van der Geer, P. *et al.* Ann Rev. Cell Biol. 10, 251-337 (1994). Polypeptide ligands known as growth factors or cytokines, are known to activate RTKs. Signaling RTKs involves ligand binding and a shift in conformation in the external domain of the receptor resulting in its dimerization. Lymboussaki, A. "Vascular Endothelial Growth Factors and their Receptors in Embryos, Adults, and in Tumors" Academic Dissertation, University of Helsinki, Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, (1999); Ullrich, A. *et al.*, Cell 61, 203-212 (1990). Binding of the ligand to the RTK results in receptor trans-phosphorylation at specific tyrosine residues and subsequent activation of the catalytic domains for the phosphorylation of cytoplasmic substrates. Id.

FLT-3 is a receptor tyrosine kinase belonging to the PDGF Receptor family expressed on acute myelogenous leukemia (AML) cells in a majority of patients and can be present in wildtype form or have activating mutations that result in constitutively active kinase function. An internal tandem repeat (ITD) mutation is expressed in about 25% of AML patients and has been associated with poor prognosis in AML patients. Levis, M. *et al.*, Blood 99, 11; 2002.

c-Kit is another receptor tyrosine kinase belonging to the PDGF Receptor family and is normally expressed in hematopoietic progenitor, mast and germ cells. C-kit expression has been implicated in a number of cancers including mast cell leukemia, germ cell tumors, small-cell lung carcinoma, gastroinstestinal stromal tumors, acute myelogenous leukemia (AML), neuroblastoma, melanoma, ovarian carcinoma, breast carcinoma. Heinrich, M. C. *et al.*, J. Clin. Onc. 20, 6 1692-1703, 2002 (review article); Smolich, B. D. *et al.*, Blood, 97, 5; 1413-1421.

c-ABL is a tyrosine kinase that was originally identified as an oncogene product from the genome of the Abelson murine leukemia virus. About 90% of chronic myelogenous

leukemia (CML), 20-30% of acute lymphoblastic leukemia (ALL) and about 1% of acute myeloblastic leukemia (AML) have a reciprocal translocation between chromosome 9 and 22. The translocation results in the 'Philadelphia' chromosome and is the reason for the expression of a chimeric BCR/ABL transcript.

FGFR3 is a tyrosine kinase associated with various cancers. Fibroblast growth factor receptor 3 (FGFR3) is a class IV receptor tyrosine kinase. FGFR3 is deregulated due to a t(4,14) translocation in about 15-20% of multiple myeloma patients. This translocation causes the expression of a functional FGFR3 that can respond to FGF1 in e.g., the bone microenvironment. In some cases, activating mutations that make FGFR3 ligand independent have been identified. These activating FGFR3 mutations have been found to cause Ras-like tumor progression and evidence exists that similar signaling pathways are utilized (Chesi, *et al.*, Blood 2001 97 729-736.).

CSF-1 (colony-stimulating factor-1) and its receptor Macrophage CSFR-1 (Fms) are required for macrophage proliferation and differentiation as well as placental development. It is expressed during pregnancy and lactation in the mammary gland. Abnormal expression of CSFR1 has been correlated with advanced stage and poor prognosis in breast cancer patients.

C-Met is a receptor tyrosine kinase that binds HGF (hepatocyte growth factor). C-Met is implicated in tumorigenesis, tumor progression and metastasis of multiple tumors including colon cancer, multiple myeloma, small and non small cell lung cancer and renal cell carcinoma. C-Met has been found mutated, amplified, and overexpressed in multiple cancers.

Two subfamilies of RTKs are specific to the vascular endothelium. These include the vascular endothelial growth factor (VEGF) subfamily and the Tie receptor subfamily. Class V RTKs include VEGFR-1, VEGFR-2, and VEGFR-3. Shibuya, M. *et al.*, Oncogene 5, 519-525 (1990); Terman, B. *et al.*, Oncogene 6, 1677-1683 (1991); Aprelikova, O. *et al.*, Cancer Res. 52, 746-748 (1992).

Members of the VEGF subfamily have been described as being able to induce vascular permeability and endothelial cell proliferation and further identified as a major inducer of angiogenesis and vasculogenesis. Ferrara, N. *et al.*, Endocrinol. Rev. 18, 4-25 (1997). VEGF is known to specifically bind to RTKs including VEGFR-1 and VEGFR-2. DeVries, C. *et al.*, Science 255, 989-991 (1992); Quinn, T. *et al.*, Proc. Natl. Acad. Sci. 90, 7533-7537 (1993). VEGF stimulates the migration and proliferation of endothelial cells and induces angiogenesis both *in vitro* and *in vivo*. Connolly, D. *et al.*, J. Biol. Chem. 264, 20017-20024 (1989); Connolly, D. *et al.*, J. Clin. Invest. 84, 1470-1478 (1989); Ferrara, N. *et*

al., Endocrino. Rew. 18, 4-25 (1997); Leung, D. *et al.*, Science 246, 1306-1309 (1989); Plouet, J. *et al.*, EMBO J 8, 3801-3806 (1989).

Because angiogenesis is known to be critical to the growth of cancer and to be controlled by VEGF and VEGF-RTK, substantial efforts have been undertaken to develop therapeutics that are antagonists of VEGF-RTK to thereby inhibit or retard angiogenesis, and, hopefully, interfere or stop tumor proliferation.

Class III RTKs are characterized by an extracellular region composed of five immunoglobulin-like domains and by a split tyrosine kinase domain. Some of the Class III RTKs which are inhibited by the compounds of Formula I include, but are not limited to, KIT, FMS, FLT3, PDGFRα, and PDGFRβ.

Class IV RTKs contain three immunoglobulin-like domains in their extracellular regions. For example, FGFR is a class IV RTK which is inhibited by the compounds of Formula I.

Examples of Class V RTKs that are inhibited by the compound of Formula I include, but are not limited to, VEGFR-1, VEGFR-2, and VEGFR-3.

As a result of inhibition of various RTKs, other ligand-stimulated cellular functions are blocked, including activation of downstream signaling molecules, cellular proliferation and survival. Agents which act as inhibitors of specific RTKs are useful in the treatment of disseminated disease and leukemia, as well as solid tumors, outside of the agent's antiangiogenic activity. That is, compounds such as those described in WO 01/60814, which have a broad range of activity at different RTKs and PTKs, are antiangiogenic agents as well as antitumor agents.

Multiple myeloma (MM), a disease of malignant B cells, is characterized by the accumulation of clonal plasma cells in the bone marrow (BM) and osteolytic bone lesions. Autologous stem cell transplant (ASCT) and advances in supportive care have had a significant impact on the disease and long-term survival. Attal, M. *et al.*, *N. Engl. J. Med.*, 1996; 335:91-97; and Barlogie, B. *et al.*, *Blood*, 1997; 89:789-793. However, patients invariably relapse, and MM remains a universal fatal disease. The identification of nonrandom chromosomal translocations in MM has resulted in the development of powerful prognostic tools and the identification of novel molecular targets. Nearly half of patients with MM overexpress a putative oncogene, dysregulated by one of five recurrent immunoglobulin heavy (IgH) translocations: 11q13 (cyclin D1), 6p21 (cyclin D3), 4p16 (FGFR3 and MMSET), 16q23 (c-maf) and 20q11 (mafB). Kuehl, W. M. *et al.*, *Nat Rev Cancer*, 2002; 2:175-187; and Avet-Loiseau, H. *et al.*, *Blood*, 2002; 99:2185-2191. These

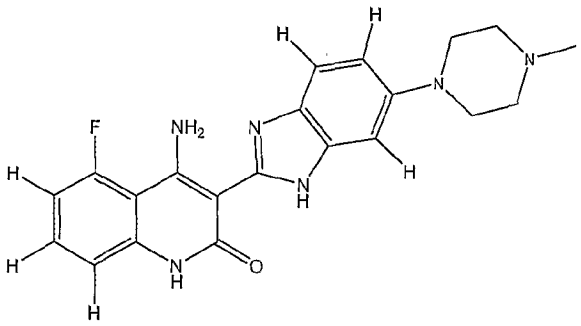
translocations likely represent an early and possibly seminal event in the development of MM. More recently, it has become clear that these specific IgH translocations impart prognostic significance. Particularly, the t(4;14) translocation with occurs in approximately 20% of patients appears to confer a particularly poor prognosis for MM, with no apparent therapeutic benefit to ASCT. Fonseca, R. *et al.*, *Blood*, 2003; 101:4569-4575; Keats, J. J. *et al.*, *Blood*, 2003; 101:1520-1529; Moreau, P. *et al.*, *Blood*, 2002; 100:1579-1583; and Chang, H. *et al.*, *Br. J. Haematol.*, 2004; 125:64-68. Clearly, novel treatment approaches are required for these patients.

The t(4;14) translocation is unusual in that it appears to dysregulate two potential oncogenes, MMSET on der(4) and FGFR3 on der(14). Chesi, M. *et al.*, *Nat. Genet.*, 1997; 16:260-265; and Chesi, M. *et al.*, *Blood*, 1998; 92:3025-3034. Whether dysregulation of either or both of these genes is critical for MM pathogenesis is not known, however several lines of evidence support a role for FGFR3 in tumor initiation and progression. Activation of WT FGFR3, a RTK, promotes proliferation and survival in myeloma cells and is weakly transforming in a hematopoetic mouse model. Plowright, E. E. *et al.*, *Blood*, 2000; 95:992-998; Chesi, M. *et al.*, *Blood*, 2001; 97:729-736; and Pollett, J. B. *et al.*, *Blood*, 2002; 100:3819-3821. Subsequent acquisition of activating mutations of FGFR3 in some MM are associated with progression to late stage myeloma and are strongly transforming in several experimental models. Chesi, M. *et al.*, *Blood*, 2001; 97:729-736; and Li, Z. *et al.*, *Blood*, 2001; 97:2413-2419. *In vitro* studies suggest that FGFR3 can impart chemoresistance, an observation supported by clinical data that demonstrate poor responses to conventional chemotherapy and shortened median survival of t(4;14) MM patients. Fonseca, R. *et al.*, *Blood*, 2003; 101:4569-4575; Keats, J. J. *et al.*, *Blood*, 2003; 101:1520-1529; Moreau, P. *et al.*, *Blood*, 2002; 100:1579-1583; and Chang, H. *et al.*, *Br. J. Haematol.*, 2004; 125:64-68. These findings suggest that ectopic expression of FGFR3 may play a significant, albeit not a singular, role in myeloma oncogenesis thus making this RTK a target for molecular based therapy.

Inhibition of FGFR3 in t(4;14) MM cell lines induces cytotoxic responses demonstrating that these cells remain dependent on FGFR3 signaling despite the complexity of genetic alterations in these cells derived from end stage patients. Trudel, S. *et al.*, *Blood*, 2004; 103:3521-3528; Paterson, J. L. *et al.*, *Br. J. Haematol.*, 2004; 124:595-603; and Grand ,E. K. *et al.*, *Leukemia*, 2004; 18:962-966. These observations are congruent with the results of receptor tyrosine inactivation in a range of human malignancies where clinical successes have been documented and encourage the clinical development of FGFR3 inhibitors for the

treatment of these poor-prognosis patients. Druker, B. J. *et al.*, *N. Engl. J. Med.*, 2001; 344:1031-1037; Demetri, G. D. *et al.*, *N. Engl. J. Med.*, 2002; 347:472-480; Slamon, D. J. *et al.*, *N. Engl. J. Med.* 2001; 344:783-792; and Smith, B. D. *et al.*, *Blood*, 2004; 103:3669-3676.

In particular, certain quinoline compounds have been shown to be useful as protein kinase inhibitors. An example quinoline inhibitor is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one, as well as tautomers and salts thereof, the structure of which is provided below as Formula I. Use and preparation of this compound and its salts, including the mono-lactic acid salt, are described in U.S. Ser. Nos. 10/982,757, 10/982,543, 10/706,328, and 10/644,055, each of which is incorporated herein by reference in its entirety. Related compounds are the subject of U.S. Pat. Nos. 6,605,617, 6,774,237, and 6,800,760, each of which is incorporated herein by reference in its entirety.



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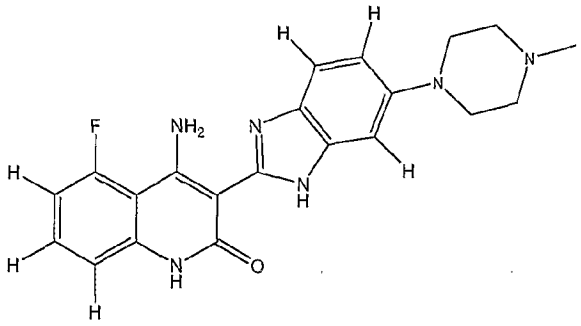
It is well known that the crystalline form of a particular drug is often an important determinant of the drug's ease of preparation, hygroscopicity, stability, solubility, storage stability, ease of formulation, rate of dissolution in the GIT fluids and *in vivo* bioavailability. Crystalline forms occur where the same composition of matter crystallizes in a different lattice arrangement resulting in different thermodynamic properties and stabilities specific to the particular crystalline form. Crystalline forms may also include different hydrates or solvates of the same compound. In deciding which form is preferable, the numerous properties of the forms are compared and the preferred form chosen based on the many physical property variables. It is entirely possible that one form can be preferable in some circumstances where certain aspects such as ease of preparation, stability, etc are deemed to be critical. In other situations, a different form may be preferred for greater dissolution rate and/or superior bioavailability.

Because improved drug formulations, showing, for example, better bioavailability or better stability are consistently sought, there is an ongoing need for new or purer polymorphic forms (i.e., crystalline forms) of existing drug molecules. The crystalline forms of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one lactic acid described herein help meet these and other needs.

SUMMARY OF THE INVENTION

The present invention provides a solid formulation of a lactic acid salt of the compound of formula I:



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for oral administration, wherein the formulation comprises a non-hydrate crystalline form of a lactic acid salt the compound of formula I.

In some embodiments, the non-hydrate crystalline form is Form A.

In some embodiments, Form A is prepared or is obtainable by stirring the compound of formula I in a solution comprising water, organic solvent and lactic acid.

In some embodiments, the organic solvent is an alcohol.

In some embodiments, the organic solvent is selected from the group consisting of ethanol and isopropanol.

In some embodiments, the solution comprises about 6.5% water.

In some embodiments, the lactic acid salt of formula I is a mono-lactic acid salt.

In some embodiments, the solid formulation is in powder form.

The present invention further provides methods of treating a patient with a powder formulation of a lactic acid salt of a compound of formula I, comprising orally administering the powder formulation, wherein the powder formulation comprises a non-hydrate crystalline form of a lactic acid salt of compound of formula I.

In some embodiments, the non-hydrate crystalline form is Form A.

In some embodiments, the patient is a cancer patient.

In some embodiments, the patient is diagnosed with multiple myeloma (MM), acute myelogenous leukemia (AML), prostate cancer, breast cancer, colon cancer, or melanoma.

In some embodiments, the patient is a refractory patient.

In some embodiments, the dose comprises 0.25 to 30 mg/kg of the lactic acid salt of the compound of formula I.

In some embodiments, the formulation is prepared or is obtainable in the form of a pill, tablet, capsule, or a caplet.

In some embodiments, the formulation is in solid form at the time of administration.

The present invention further provides a crystalline form (Form A) of a lactic acid salt of the compound of formula I wherein the crystalline form, has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 5.7° and about 25.9°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at about 15.9°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at about 12.4°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at about 17.0°.

The present invention further provides a crystalline form (Form A) of a lactic acid salt of the compound of formula I wherein the crystalline form, has an X-ray powder diffraction pattern comprising at least 3 characteristic peaks, in terms of 2θ, selected from at about 5.7, about 11.3, about 12.4, about 15.3, about 15.9, about 17.0, about 19.1, about 19.7, about 20.5, about 20.9, about 22.8, about 23.4, about 23.7, about 24.7, about 25.0, about 25.9, about 26.9, and about 31.2 degrees.

In some embodiments, the crystalline form has an X-ray powder diffraction pattern substantially as shown in Figure 1.

In some embodiments, the crystalline form has a differential scanning calorimetry thermogram showing an endotherm at about 213 °C.

In some embodiments, the crystalline form has a differential scanning calorimetry thermogram substantially as shown in Figure 2.

The present invention further provides compositions comprising crystalline Form A.

In some embodiments, at least about 50% by weight of total lactic acid salt of the compound of formula I in the composition is present as Form A.

In some embodiments, at least about 70% by weight of total lactic acid salt of the compound of formula I in the composition is present as Form A.

In some embodiments, at least about 80% by weight of total lactic acid salt of the compound of formula I in the composition is present as Form A.

In some embodiments, at least about 90% by weight of total lactic acid salt of the compound of formula I in the composition is present as Form A.

In some embodiments, at least about 95% by weight of total lactic acid salt of the compound of formula I in the composition is present as Form A.

In some embodiments, at least about 97% by weight of total lactic acid salt of the compound of formula I in the composition is present as Form A.

In some embodiments, at least about 98% by weight of total lactic acid salt of the compound of formula I in the composition is present as Form A.

In some embodiments, at least about 99% by weight of total lactic acid salt of the compound of formula I in the composition is present as Form A.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

In some embodiments, the composition consists essentially of the lactic acid salt of the compound of formula I wherein at least 95% by weight of the lactic acid salt of the compound of formula I is present in the composition as the Form A.

In some embodiments, the composition consists essentially of the lactic acid salt of the compound of formula I wherein at least 97% by weight of the lactic acid salt of the compound of formula I is present in the composition as the Form A.

In some embodiments, the composition consists essentially of the lactic acid salt of the compound of formula I wherein at least 98% by weight of the lactic acid salt of the compound of formula I is present in the composition as the Form A.

In some embodiments, the composition consists essentially of the lactic acid salt of the compound of formula I wherein at least 99% by weight of the lactic acid salt of the compound of formula I is present in the composition as the Form A.

The present invention further provides methods of preparing crystalline Form A comprising stirring the compound of formula I in a solution comprising water, organic solvent and lactic acid.

In some embodiments, organic solvent is an alcohol.

In some embodiments, organic solvent is selected from the group consisting of ethanol and isopropanol.

In some embodiments, the solution comprises about 6.5% water.

The present invention further provides a crystalline form prepared by any one of the methods described herein.

The present invention further provides a crystalline hydrate of a lactic acid salt of a compound of Formula I.

In some embodiments of the crystalline hydrates of the invention, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I is about 1 or about 6.

In some embodiments of the crystalline hydrates of the invention, the hydrate is a monohydrate or hexahydrate.

In some embodiments of the crystalline hydrates of the invention, the lactic salt is a is a mono-lactic acid salt.

The present invention provides a crystalline hydrate (Form B) of a lactic acid salt of a compound of Formula I wherein the crystalline form has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 17.6°, about 19.3° and about 26.0°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 23.3°, about 23.5° and about 28.2°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 11.9°, about 15.3°, about 16.1°, and about 18.5°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 10.2° and about 12.9°.

In some embodiments, the X-ray powder diffraction pattern comprises at least 3 characteristic peaks, in terms of 2θ, selected from:

at about 10.2, about 11.3, about 11.6, about 11.9, about 12.9, about 15.3, about 15.6, about 16.1, about 17.6, about 18.5, about 19.3, about 22.3, about 23.3, about 23.5, about 23.9, about 26.0, about 28.2, about 29.3, about 29.8, about 30.7, about 32.2, about 32.6, about 33.1 and about 34.3 °.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 6.

In some embodiments, the crystalline form has a differential scanning calorimetry thermogram showing an endotherm at about 155 °C.

In some embodiments, the crystalline form has a differential scanning calorimetry thermogram substantially as described herein.

The present invention further provides compositions comprising crystalline hydrates of a lactic acid salt of a compound of Formula I.

In some embodiments, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I is about 1 or about 6.

In some embodiments, the hydrate is a monohydrate or hexahydrate.

In some embodiments, the lactic salt is a is a mono-lactic acid salt.

The present invention further provides compositions comprising crystalline Form B.

In some embodiments, at least about 50% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form B.

In some embodiments, at least about 70% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form B.

In some embodiments, at least about 80% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form B.

In some embodiments, at least about 90% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form B.

In some embodiments, at least about 95% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form B.

In some embodiments, at least about 99% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form B.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

The present invention further provides methods of preparing crystalline Form B comprising suspending Form A in a solution comprising water and an organic solvent at a temperature of about 20 °C to about 60°C, wherein said water is present in said solution in an amount of about 5% to about 20% by volume.

In some embodiments, the organic solvent comprises an alcohol, a ketone, an organic nitrile, or mixture thereof.

In some embodiments, the organic solvent comprises one or more of ethanol, acetone, methyl ethyl ketone, and acetonitrile.

In some embodiments, Form B is prepared by suspending Form A in a solution comprising water and an organic solvent at a temperature of about 20 °C to about 60°C, wherein said water is present in said solution in an amount of about 5% to about 20% by volume.

The present invention further provides a crystalline hydrate (Form C) wherein the crystalline form has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at from about 3.2° to about 3.6°, at from about 6.5° to about 7.1°, and at from about 9.8° to about 10.6°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at from about 13.3° to about 14.1°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at about 27.3 to about 27.5°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at from about 17.6° to about 17.8°, and at from about 24.7° to about 24.9°.

In some embodiments, the X-ray powder diffraction pattern comprises at least 3 characteristic peaks, in terms of 2θ, selected from:

at from about 3.2 to about 3.6, at from about 6.5 to about 7.1, at from about 9.8 to about 10.6, at from about 13.3 to about 14.1, at from about 17.6 to about 17.8, at about 18.8, at about 20.2, at from about 24.7 to about 24.9, at about 27.3 to about 27.5, at about 28.0, and at from about 29.0 to about 29.3°.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 7 or as described herein.

In some embodiments, the crystalline hydrate of has a differential scanning calorimetry thermogram showing a prominent endotherm at about 150 °C.

In some embodiments, the crystalline hydrate of has a differential scanning calorimetry thermogram substantially as described herein.

The present invention further provides compositions comprising crystalline Form C.

In some embodiments, at least about 50% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form C.

In some embodiments, at least about 70% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form C.

In some embodiments, at least about 80% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form C.

In some embodiments, at least about 90% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form C.

In some embodiments, at least about 95% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form C.

In some embodiments, at least about 99% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form C.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

The present invention further provides methods of preparing crystalline Form C comprising contacting the amorphous form of said lactic acid salt of said compound of Formula I with a relative humidity of from about 50% to about 75% at a temperature of from about 40 °C to about 80 °C.

In some embodiments, the contacting is performed for at least about 6 hours.

In some embodiments, Form C is prepared by contacting the amorphous form of said lactic acid salt of said compound of Formula I with a relative humidity of from about 50% to about 75% at a temperature of from about 40 °C to about 80 °C.

The present invention further provides methods of preparing a crystalline hydrate of a lactic acid salt of a compound of Formula I comprising diffusing organic solvent vapor into an aqueous solution of said lactic acid salt of said compound of Formula I at a temperature of about 0 °C to about 10 °C.

In some embodiments, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I in the crystalline hydrate is about 1 or about 6.

In some embodiments, the crystalline hydrate is a monohydrate or hexahydrate.

In some embodiments, the lactic salt in the crystalline hydrate is a is a mono-lactic acid salt.

In some embodiments, the crystalline hydrate is Form C.

In some embodiments, the organic solvent comprises an organic nitrile.

In some embodiments, the organic nitrile is acetonitrile.

In some embodiments, the temperature is about 5 °C.

In some embodiments, a crystalline hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of diffusing organic solvent vapor into an aqueous solution of said lactic acid salt of said compound of Formula I at a temperature of about 0 °C to about 10 °C.

In some embodiments, a crystalline hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of diffusing organic solvent vapor into an aqueous solution of said lactic acid salt of said compound of Formula I at a temperature of about 0 °C to about 10 °C.

In some embodiments, a crystalline hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of diffusing organic solvent vapor into an aqueous solution of said lactic acid salt of said compound of Formula I at a temperature of about 0 °C to about 10 °C, wherein the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I in the crystalline hydrate is about 1 or about 6.

In some embodiments, a crystalline hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of diffusing organic solvent vapor into an aqueous solution of said lactic acid salt of said compound of Formula I at a temperature of about 0 °C to about 10 °C, wherein the crystalline hydrate is a monohydrate or hexahydrate.

In some embodiments, a crystalline hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of diffusing organic solvent vapor into an aqueous solution of said lactic acid salt of said compound of Formula I at a temperature of about 0 °C to about 10 °C, wherein the lactic salt in the crystalline hydrate is a is a mono-lactic acid salt.

In some embodiments, Form C is prepared by the method of diffusing organic solvent vapor into an aqueous solution of said lactic acid salt of said compound of Formula I at a temperature of about 0 °C to about 10 °C, wherein the lactic salt in the crystalline hydrate is a is a mono-lactic acid salt.

The present invention provides a crystalline hydrate (Form D) of a lactic acid salt of a compound of Formula I wherein the crystalline form has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 4.0° and at about 27.2°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at about 22.0°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 14.3° and at about 16.4°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 8.0° and at about 20.1°.

In some embodiments, the X-ray powder diffraction pattern comprises at least 3 characteristic peaks, in terms of 2θ, selected from:

at about 4.0, about 8.0, about 11.5, about 12.0, about 14.3, about 15.8, about 16.4, about 20.1, about 21.2, about 22.0, about 23.6, about 27.2 and about 27.9 degrees.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 8.

In some embodiments, the crystalline form has a differential scanning calorimetry thermogram showing an endotherm at about 73 °C, an endotherm at about 145 °C, an exotherm at about 160 °C, and an endotherm at about 189 °C.

In some embodiments, the crystalline form has a differential scanning calorimetry thermogram substantially as described herein.

The present invention further provides compositions comprising crystalline Form D.

In some embodiments, at least about 50% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form D.

In some embodiments, at least about 70% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form D.

In some embodiments, at least about 80% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form D.

In some embodiments, at least about 90% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form D.

In some embodiments, at least about 95% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form D.

In some embodiments, at least about 99% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form D.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

The present invention further provides methods of preparing crystalline Form D comprising contacting the amorphous form of said lactic acid salt of said compound of Formula I with an inert atmosphere having a relative humidity of about 30% or less at a temperature of from about 80 °C to about 150 °C.

In some embodiments, the temperature is about 120 °C.

In some embodiments, the contacting is performed for at least about 5 hours.

In some embodiments, a hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of contacting the amorphous form of said lactic acid salt of said compound of Formula I with an inert atmosphere having a relative humidity of about 30% or less at a temperature of from about 80 °C to about 150 °C.

In some embodiments, Form D is prepared by the method of contacting the amorphous form of said lactic acid salt of said compound of Formula I with an inert atmosphere having a relative humidity of about 30% or less at a temperature of from about 80 °C to about 150 °C.

The present invention further provides a crystalline hydrate (Form E) of a lactic acid salt of a compound of Formula I wherein the crystalline form has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 13.4° and at about 25.5°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 22.6°, at about 24.1°, at about 25.0°, and at about 27.7°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 12.1° and at about 18.1°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 6.1° and at about 8.4°.

In some embodiments, the X-ray powder diffraction pattern comprises at least 3 characteristic peaks, in terms of 2θ, selected from:

at about 6.1, about 8.4, about 8.7, about 12.1, about 13.4, about 14.9, about 18.1, about 19.0, about 20.1, about 21.1 about 21.5, about 22.6, about 24.1, about 24.5, about 25.0, about 25.5, about 27.7, about 30.1, and about 30.6 degrees.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 9.

In some embodiments, the crystalline form has a differential scanning calorimetry thermogram showing an endotherm at about 76 °C, and an endotherm at about 128 °C.

In some embodiments, the crystalline form has a differential scanning calorimetry thermogram substantially as described herein.

The present invention further provides compositions comprising crystalline Form E.

In some embodiments, at least about 50% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form E.

In some embodiments, at least about 70% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form E.

In some embodiments, at least about 80% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form E.

In some embodiments, at least about 90% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form E.

In some embodiments, at least about 95% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form E.

In some embodiments, at least about 99% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form E.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

The present invention further provides methods of preparing crystalline Form E comprising suspending Form A in water.

In some embodiments, a hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of suspending Form A in water.

In some embodiments, Form E is prepared by the method of suspending Form A in water.

The present invention further provides methods of preparing crystalline Form E comprising seeding an aqueous solution of a lactic acid salt of the compound of Formula I with seed crystals of crystalline Form E, wherein the concentration of said solution is about 100 to about 200 mg/mL.

In some embodiments, a hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of seeding an aqueous solution of a lactic acid salt of the compound of Formula I with seed crystals of crystalline Form E, wherein the concentration of said solution is about 100 to about 200 mg/mL.

In some embodiments, Form E is prepared by the method of seeding an aqueous solution of a lactic acid salt of the compound of Formula I with seed crystals of crystalline Form E, wherein the concentration of said solution is about 100 to about 200 mg/mL.

The present invention further provides methods of preparing crystalline Form E comprising crystallizing a lactic acid salt of the compound of Formula I in a solvent, wherein the solvent comprises about 1 to about 10% by volume of water and about 90 to about 99% by volume of an organic solvent.

In some embodiments, the solvent comprises about 4% by volume of water.

In some embodiments, the organic solvent comprises THF or ethyl acetate.

In some embodiments, crystallizing Form B is facilitated by suspending the amorphous form of a lactic acid salt of said compound of Formula I in a solvent, at a temperature of about 5 °C, for a time of at least about 5 days, wherein said solvent comprises about 5% water by volume and about 95% acetonitrile by volume.

The present invention further provides methods of preparing crystalline Form E comprising adding an aqueous solution of a lactic acid salt of a compound of Formula I to a solvent at a temperature of about 2°C to about 30 °C, wherein the concentration of the

aqueous solution is about 100 to about 400 mg/mL, and the solvent comprises ethyl acetate and tetrahydrofuran.

In some embodiments, the ratio of the aqueous solution to the ethyl acetate to the tetrahydrofuran is about 1:10:5 by volume.

In some embodiments, a hydrate of a lactic acid salt of a compound of Formula I is prepared by the method of adding an aqueous solution of a lactic acid salt of a compound of Formula I to a solvent at a temperature of about 2°C to about 30 °C, wherein the concentration of the aqueous solution is about 100 to about 400 mg/mL, and the solvent comprises ethyl acetate and tetrahydrofuran.

In some embodiments, Form E is prepared by the method of adding an aqueous solution of a lactic acid salt of a compound of Formula I to a solvent at a temperature of about 2°C to about 30 °C, wherein the concentration of the aqueous solution is about 100 to about 400 mg/mL, and the solvent comprises ethyl acetate and tetrahydrofuran.

The present invention also provides for solid compositions (i.e., formulations) for oral administration containing a crystalline hydrate form of a lactic acid salt of the compound of Formula I .

In some embodiments, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I in the crystalline hydrate is about 1 or about 6.

In some embodiments, the crystalline hydrate is a monohydrate or hexahydrate.

In some embodiments, the lactic salt in the crystalline hydrate is a is a mono-lactic acid salt.

In some embodiments, the crystalline hydrate is Form B.

In some embodiments, the crystalline hydrate is Form C.

In some embodiments, the crystalline hydrate is Form D.

In some embodiments, the crystalline hydrate is Form E.

In some embodiments, the formulation is in the form of a powder.

In some embodiments, the crystalline hydrate remains substantially intact under ambient conditions for a period greater than about 36 hours.

In some embodiments, the crystalline hydrate remains substantially intact under ambient conditions for a period greater than about 1 week.

In some embodiments, the crystalline hydrate remains substantially intact under ambient conditions for a period greater than about 1 month.

In some embodiments, the crystalline hydrate remains substantially intact under ambient conditions for a period greater than about 6 months.

In some embodiments, the crystalline hydrate remains substantially intact under ambient conditions for a period greater than about 1 year.

The present invention also provides a dosage form which contains solid formulations described herein containing a crystalline hydrate form of a lactic acid salt of the compound of Formula I .

In some embodiments, the dosage form is a pill, tablet, capsule, or caplet.

The present invention further provides methods of treating a patient comprising administering to the patient a formulation comprising a crystalline hydrate form of a lactic acid salt of the compound of Formula I .

In some embodiments, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I in the crystalline hydrate is about 1 or about 6.

In some embodiments, the crystalline hydrate is a monohydrate or hexahydrate.

In some embodiments, the lactic salt in the crystalline hydrate is a is a mono-lactic acid salt.

In some embodiments, the crystalline hydrate is Form B.

In some embodiments, the crystalline hydrate is Form C.

In some embodiments, the crystalline hydrate is Form D.

In some embodiments, the crystalline hydrate is Form E.

In some embodiments, the patient is a cancer patient.

In some embodiments, the patient has been diagnosed with multiple myeloma (MM), acute myelogenous leukemia (AML), prostate cancer, breast cancer, colon cancer, or melanoma.

In some embodiments, the patient is a refractory patient.

In some embodiments, the patient is treated with a dose that is less than the maximum tolerated dose (MTD). In further embodiments, the dose comprises 0.25 to 30 mg/kg of the lactic acid salt of the compound of formula I.

In some embodiments, the formulation is in solid form at the time of administration.

The present invention further provides a mesomorphic form (Form H) of a hydrate of lactic acid salt of the compound of Formula I wherein the mesomorphic form has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 3.5° and at about 26.4°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at about 16.7°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at about 20.6°.

In some embodiments, the X-ray powder diffraction pattern further comprises a characteristic peak, in terms of 2θ, at about 6.9°.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 12.

The present invention further provides methods of preparing the mesomorphic Form H, comprising adding an aqueous solution of a lactic acid salt of the compound of Formula I to a solvent at a temperature of about 0 to about 10 °C, wherein the concentration of the aqueous solution is about 100 to about 350 mg/mL; and the solvent comprises acetonitrile.

In some embodiments, the ratio of the aqueous solution to the acetonitrile is about 1:10 by volume.

In some embodiments, the mixture obtained by the addition is allowed to stand at about 0 to about 10 °C for at least about 24 hours.

In some embodiments, the mixture obtained by the addition is allowed to stand at about 2 °C for at least about 24 hours.

In some embodiments, Form H is prepared by the method of adding an aqueous solution of a lactic acid salt of the compound of Formula I to a solvent at a temperature of about 0 to about 10 °C, wherein the concentration of the aqueous solution is about 100 to about 350 mg/mL; and the solvent comprises acetonitrile.

The present invention further provides methods of preparing the mesomorphic Form H,, comprising evaporating an aqueous solution of a lactic acid salt of the compound of Formula I at a temperature of about 20 to about 30 °C.

In some embodiments, Form H is prepared by the method of evaporating an aqueous solution of a lactic acid salt of the compound of Formula I at a temperature of about 20 to about 30 °C.

In some embodiments of Form H, the lactic acid salt of said compound of Formula I is a mono-lactic acid salt.

The present invention further provides compositions comprising mesomorphic Form H.

In some embodiments, at least about 50% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form H.

In some embodiments, at least about 70% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form H.

In some embodiments, at least about 80% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form H.

In some embodiments, at least about 90% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form H.

In some embodiments, at least about 95% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form H.

In some embodiments, at least about 99% by weight of hydrate of lactic acid salt of the compound of formula I in the composition is present as Form H.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

The present invention provides a crystalline hydrate (Form I) of a lactic acid salt of a compound of Formula I wherein the crystalline form has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 2.3° and at about 11.9°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 9.8° and about 15.7°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 8.1° and about 21.5°.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 13.

In some embodiments, the lactic acid salt is a mono-lactic acid salt.

The present invention further provides compositions comprising crystalline Form I.

In some embodiments, the composition further comprises water.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

The present invention further provides methods of treating a patient comprising administering to the patient a pharmaceutical formulation containing crystalline Form I .

In some embodiments, the patient is a cancer patient.

In some embodiments, the patient has been diagnosed with multiple myeloma (MM), acute myelogenous leukemia (AML), prostate cancer, breast cancer, colon cancer, or melanoma.

In some embodiments, the patient is a refractory patient.

The present invention further provides a method of preparing Form I comprising combining Form A with a solvent containing at least about 50 % by volume of water.

In some embodiments, Form I is prepared by the method of combining Form A with a solvent containing at least about 50 % by volume of water.

The present invention further provides a crystalline solvate of a lactic acid salt of the compound of Formula I.

In some embodiments, the solvate is a 1,4-dioxane-solvate.

The present invention further provides a crystalline 1,4-dioxane-solvate of a lactic acid salt of the compound of Formula I wherein the solvate has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 5.2° and at about 25.0°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 21.2° and about 15.2°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 10.4° and about 26.0°.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 10.

In some embodiments, the solvate is a hemisolvate.

The present invention further provides compositions comprising a crystalline solvate of a lactic acid salt of the compound of Formula I.

In some embodiments, the solvate is a 1,4-dioxane-solvate.

The present invention further provides compositions comprising a crystalline 1,4-dioxane-solvate of a lactic acid salt of the compound of Formula I wherein the solvate has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 5.2° and at about 25.0°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 21.2° and about 15.2°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 10.4° and about 26.0°.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 10.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

The present invention further provides methods of preparing a crystalline 1,4-dioxane-solvate of a lactic acid salt of the compound of Formula I comprising crystallizing the 1,4-dioxane-solvate from a solution containing 1,4-dioxane.

In some embodiments, a crystalline 1,4-dioxane-solvate of a lactic acid salt of the compound of Formula I is prepared by the method of crystallizing the 1,4-dioxane-solvate from a solution containing 1,4-dioxane.

In some embodiments, the solvate is a mono-lactic acid salt.

The present invention further provides a crystalline benzene-solvate of a lactic acid salt of the compound of Formula I.

In some embodiments, the solvate is a hemisolvate.

In some embodiments, the solvate is a mono-lactic acid salt.

The present invention further provides a crystalline benzene-solvate of a lactic acid salt of the compound of Formula I wherein the solvate has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 5.4° and at about 24.7°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 10.3° and about 21.5°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 15.2° and about 27.3°.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 11.

In some embodiments, the solvate is a hemisolvate.

The present invention further provides compositions comprising a crystalline benzene-solvate of a lactic acid salt of the compound of Formula I.

The present invention further provides compositions comprising a crystalline benzene-solvate of a lactic acid salt of the compound of Formula I wherein the solvate has an X-ray powder diffraction pattern comprising characteristic peaks, in terms of 2θ, at about 5.4° and at about 24.7°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 10.3° and about 21.5°.

In some embodiments, the X-ray powder diffraction pattern further comprises characteristic peaks, in terms of 2θ, at about 15.2° and about 27.3°.

In some embodiments, the X-ray powder diffraction pattern is substantially as shown in Figure 11.

In some embodiments, the solvate is a hemisolvate.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

The present invention further provides methods preparing a crystalline benzene-solvate of a lactic acid salt of the compound of Formula I comprising crystallizing the crystalline benzene-solvate from a solution comprising benzene.

In some embodiments, a crystalline benzene-solvate of a lactic acid salt of the compound of Formula I is prepared by crystallizing the crystalline benzene-solvate from a solution comprising benzene.

The present invention further provides any crystalline form described herein or formulation thereof for use in therapy.

The present invention further provides any crystalline form described herein or formulation thereof for use in the preparation of a medicament for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an XRPD pattern characteristic of Form A.

Figure 2 shows a DSC thermogram characteristic of Form A.

Figure 3 shows a DVS cycle (mass change v. time) characteristic of Form A.

Figure 4 shows a DVS cycle (mass change v. RH) characteristic of Form A.

Figure 5 shows an XRPD pattern characteristic of the amorphous form.

Figure 6 shows an XRPD pattern characteristic of Form B.

Figure 7 shows an XRPD pattern characteristic of Form C.

Figure 8 shows an XRPD pattern characteristic of Form D.

Figure 9 shows an XRPD pattern characteristic of Form E.

Figure 10 shows an XRPD pattern characteristic of Form F.

Figure 11 shows an XRPD pattern characteristic of Form G.

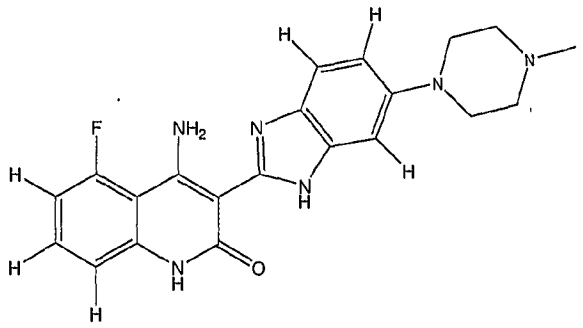
Figure 12 shows an XRPD pattern characteristic of Form H.

Figure 13 shows an XRPD pattern characteristic of Form I.

DETAILED DESCRIPTION

Non-hydrate Crystalline Forms: Form A

In a first aspect, the present invention provides, *inter alia*, formulations, such as solid (e.g., powder) formulations for oral administration, of a lactic acid salt of the compound of formula I:



I

A lactic acid salt which is present in the formulations of the invention contains a non-hydrate crystalline form of the lactic acid salt of the compound of formula I. By "non-hydrate crystalline form" is meant any lactic acid salt of the compound of formula I which is in substantially anhydrous form or non-solvated form, including both hygroscopic, slightly hygroscopic, and non-hygroscopic anhydrous forms. Lactic acid salts can further include mono- and di-acid salt forms, and the like. Preferably, the lactic acid salt is a mono-lactic acid salt of the compound of formula I. Di-lactic acid salts (i.e., bis-lactic acid salts), tri-lactic acid salts (i.e., tris-lactic acid salts) and intermediate and higher orders of salts are also encompassed and can be formed by the combination of greater than one equivalent of lactic acid with the compound of formula I according to routine methods of preparing acid addition salts.

In some embodiments, the non-hydrate crystalline form of the lactic acid salt of the compound of formula I is crystalline Form A. Form A can be characterized by any one or more solid state techniques such as X-ray powder diffraction (XRPD), single crystal X-ray diffraction, differential scanning calorimetry (DSC), dynamic vapor sorption (DVS), crystal morphology, solid state nuclear magnetic resonance, Raman scattering, infrared (IR) spectroscopy, and the like. In some embodiments, Form A can be identified by its XRPD pattern. In some embodiments, Form A can be identified by its DSC thermogram. In some embodiments, Form A can be identified by crystal morphology. In some embodiments, Form A can be identified by its DVS cycle. Other techniques, alone or in combination with the ones recited herein, can also be used to identify Form A.

Crystalline Form A is characterized as an anhydrous, non-hygroscopic crystalline form of the mono-lactic acid salt of the compound of formula I. Form A can be identified by its X-ray powder diffraction (XRPD) pattern which is provided in Figure 1. In some embodiments, the crystalline form of the invention has an XRPD pattern substantially as shown in Figure 1 (two-theta values provided in Example 3), where the term "substantially"

in this instance indicates that two-theta values for individual peaks can vary about ±0.2°. The relative intensities of the peaks can also vary, depending upon the sample preparation technique, the sample mounting procedure and the particular instrument employed. Powder X-ray diffraction two-theta data consistent with Form A is provided in Example 3 below. As discussed above, many factors can affect the 2-theta values. Therefore, the peak assignments listed in Example 3 can vary by plus or minus about 0.2°.

The crystalline Form A of the invention can be further recognized by its differential scanning calorimetry (DSC) thermogram which has a characteristic endothermic peak 210 °C. A typical DSC thermogram for a sample containing substantially pure Form A is provided in Figure 2. In some embodiments, the crystalline form of the invention has a DSC trace substantially as shown in Figure 2, where the term "substantially" in this instance indicates that features such as endotherms, exotherms, baseline shifts, etc. can vary about ± 4 °C. For DSC, it is known that the temperatures observed will depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms can vary by plus or minus about 4 °C.

Sorption/desorption data according to dynamic vapor sorption techniques, such as provided in Example 3 and Figures 3 and 4, further indicate that Form A can be characterized as a non-hygroscopic material.

Crystalline Form A can be prepared by any of numerous methods in the art. In some embodiments, Form A can be prepared by combining the compound of formula I with lactic acid in a solvent and precipitating crystalline Form A from the resulting solution. In some embodiments, the molar ratio of compound of formula I to lactic acid is about 10:1 to about 1:10, about 5:1 to about 1:5, about 2:1 to about 1:2, or about 1:1.

An example method for preparing Form A is as follows:

(a) suspending the compound of formula I (or the tautomers thereof) in a solvent or mixture of solvents;

(b) contacting lactic acid with the compound of formula I to provide a mixture;

(c) heating the mixture;

(d) cooling the mixture; and

(e) isolating Form A.

In some embodiments, the mixture is heated and refluxed prior to cooling. In further embodiments, the isolating step includes filtering the mixture. In further embodiments, the

lactic acid may be a mixture of the D and L forms of lactic acid or may be the D lactic acid or the L lactic acid.

Suitable solvents include organic solvents, such as organic solvents that can at least partially dissolve the lactic acid salt of the compound of formula I. Example organic solvents include alcohols (e.g., methanol, ethanol, ispropanol, glycols, etc.), ketones (e.g., acetone, methylethyl ketone, etc.), nitriles (e.g., acetonitrile, propionitril, etc.), hydrocarbons (heptane, hexanes, pentane, benzene, toluene, etc.), halogenated hydrocarbons (e.g., dichloromethane and the like), ethers (diethyl ether, methyl-t-butyl ether, tetrahydrofuran, etc.), dimethylformamide, dimethylsulfoxide, mixtures thereof, and the like. Suitable solvents can further include mixtures of organic solvents and water. In some embodiments, the weight percent of water in the organic solvent is less than about 10%, less than about 9%, less than about 8%, less than about 7%, less than about 6%, less than about 5%, less than about 4%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, less than about 0.5%, or less than about 0.2%. In some embodiments, the solvent used in the method of preparing the salt is a protic solvent. In other embodiments of the invention, the solvent used in the method of preparing the salt is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, 2-butanol, acetone, butanone, dioxanes, water, tetrahydrofuran, and combinations of these. In some embodiments, the solvent contains an alcohol such as ethanol or isopropanol. In some embodiments, the solvent contains a mixture of alcohol and water such as, for example, less than about 10% water, less than about 7.5% water, 6.5% water, less than about 5% water, less than about 2.5% water, or less than about 1% water. In some embodiments, the solvent is acetone. In some embodiments, the solvent is tetrahydrofuran optionally containing water (e.g., about 10% by weight). In some embodiments, the solvent is acetonitrile. In some embodiments, the solvent is heptane containing 1% Tween 80. In some embodiments, the solvent is toluene.

Precipitation of crystalline Form A of the invention from solution can be carried out by any suitable manner according to routine methods. For example, solutions of a lactic acid salt of the compound of Formula I can be evaporated, cooled, treated with antisolvent, or combinations thereof. Treatment with antisolvent can be carried out by layering or vapor diffusion techniques. Suitable antisolvents include organic solvents, as well as water, that are miscible with the crystallizing solvent, yet are relatively poor solvents for the subject compound.

The methods for preparation of Form A provided herein can result in substantially pure Form A (e.g., compositions containing less than about 20%, about 10%, about 5%, or about 3% by weight of impurities, amorphous material and/or other crystalline forms) as well as mixtures enriched in Form A (e.g., mixtures containing greater than about 50% by weight Form A relative to, for example, impurities, amorphous material or other crystalline forms). Accordingly, the present invention further provides compositions containing Form A. In some embodiments, at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% by weight of total lactic acid salt of the compound of formula I in a composition is present as Form A. In further embodiments, compositions of the present invention consist essentially of a lactic acid salt of the compound of formula I where at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the lactic acid salt of the compound of formula I is present in the composition as Form A. In further embodiments, compositions of the present invention consist essentially of a lactic acid salt of the compound of formula I where at least about 98.0%, at least about 98.1%, at least about 98.2%, at least about 98.3%, at least about 98.4%, at least about 98.5%, at least about 98.6%, at least about 98.7%, at least about 98.8%, at least about 98.9%, at least about 99.0%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, at least about 99.8%, at least about 99.9%, of the lactic acid salt of the compound of formula I is present in the composition as Form A. In some embodiments, the remainder lactic acid salt of the compound of formula I is present in amorphous form or one or more other crystalline forms (including solvates and hydrates). Amounts of different crystalline forms of in a composition can be determined by routine spectroscopic methods, such as X-ray powder diffraction, DSC, and the like.

The instant invention also provides for solid compositions (i.e., formulations) containing a non-hydrate crystalline form of a lactic acid salt of the compound of Formula I (e.g., Form A) with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, to treat or ameliorate a variety of disorders related to the activity of VEGF-RTK, more particularly for example, angiogenesis associated with cancer. Pharmaceutically acceptable excipients, diluents, binders, carriers and the like include, but are not limited to, microcrystalline cellulose, lactose, dibasic calcium phosphate, tribasic calcium phosphate, sodium starch glycolate (NaSG), crospovidone, crosscarmellose (CC), sodium lauryl sulfate (SLS), Tween, polyethylene glycol (PEG), povidone, hydroxypropyl cellulose (HPMC), Mg stearate, Ca stearate, stearic acid, sodium stearate fumarate, and silicon dioxide. In some

embodiments, the compositions are in powder form suitable for compaction, tableting, and/or oral administration.

In some embodiments, the solid compositions of the invention include a therapeutically effective dose of a non-hydrate crystalline form of a lactic acid salt of the compound of formula I (e.g., Form A). A therapeutically effective dose refers to that amount of lactic acid salt of the compound of formula I sufficient to result in amelioration of symptoms of a given disorder. The solid pharmaceutical compositions of the instant invention can be manufactured by methods well known in the art such as conventional granulating, mixing, dissolving, encapsulating, lyophilizing, emulsifying or levigating processes, among others. The solid compositions can be in the form of, for example, granules, powders, tablets, or capsules. The instant compositions can be formulated for various routes of administration, for example, by oral administration, by transmucosal administration, and subcutaneous administration.

In order to determine the amount of compound in a patient following administration, certain manipulative steps can be taken. Such a method is described in the U.S. Provisional Application Serial No. 60/517,915, titled, "Methods of Treating Cancer and Related Methods" filed on November 7, 2003, by Vora *et al.* incorporated by reference in its entirety herein.

Oral, buccal, and sublingual administration, powders, suspensions, granules, tablets, pills, capsules, gelcaps, and caplets are acceptable as solid dosage forms. These can be prepared, for example, by mixing a non-hydrate crystalline form of a lactic acid salt of the compound of formula I (e.g., Form A) with at least one additive or excipient such as a starch or other additive. Suitable additives or excipients are sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, sorbitol, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides, methyl cellulose, hydroxypropylmethyl-cellulose, and/or polyvinylpyrrolidone. Optionally, oral dosage forms can contain other ingredients to aid in administration, such as an inactive diluent, or lubricants such as magnesium stearate, or preservatives such as paraben or sorbic acid, or anti-oxidants such as ascorbic acid, tocopherol or cysteine, a disintegrating agent, or chelating agents such as EDTA, binders, thickeners, buffers, sweeteners, flavoring agents or perfuming agents. Additionally, dyestuffs or pigments may be added for identification. Tablets and pills may be further treated with suitable coating materials known in the art, such as moisture protective, enteric, or sustained release coatings.

In some embodiments, the compositions are supplied in a powder form in a storage container such as a vial In some embodiments, the vial is closed and in other embodiments the vial can be evacuated with an inert gas and stoppered.

Besides those representative dosage forms described above, pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant invention. Such excipients and carriers are described, for example, in "Remingtons Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991), which is incorporated herein by reference.

The formulations of the invention may be designed for to be short-acting, fast-releasing, long-acting, and sustained-releasing as described below. Thus, the pharmaceutical formulations may also be formulated for controlled release or for slow release.

The instant compositions may also comprise, for example, micelles or liposomes, or some other encapsulated form, or may be administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the pharmaceutical formulations may be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections or as implants such as stents. Such implants may employ known inert materials such as silicones and biodegradable polymers.

Specific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs. Any of the above dosage forms containing effective amounts are well within the bounds of routine experimentation and therefore, well within the scope of the instant invention.

A therapeutically effective dose may vary depending upon the route of administration and dosage form. The non-hydrate crystalline form of a lactic acid salt of the compound of Formula I (e.g., Form A) can be provided in a formulation that exhibits a high therapeutic index. The therapeutic index is typically understood to be the dose ratio between toxic and therapeutic effects which can be expressed as the ratio between LD_{50} and ED_{50}. The LD_{50} is the dose lethal to 50% of the population and the ED_{50} is the dose therapeutically effective in 50% of the population. The LD_{50} and ED_{50} are determined by standard pharmaceutical procedures in animal cell cultures or experimental animals.

"Treating" within the context of the instant invention, means an alleviation of symptoms associated with a disorder or disease, or halt of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder. For example, within the context of treating patients in need of an inhibitor of VEGF-RTK, successful treatment may

include a reduction in the proliferation of capillaries feeding a tumor or diseased tissue, an alleviation of symptoms related to a cancerous growth or tumor, proliferation of capillaries, or diseased tissue, a halting in capillary proliferation, or a halting in the progression of a disease such as cancer or in the growth of cancerous cells. Treatment may also include administering the solid pharmaceutical formulations of the present invention in combination with other therapies. For example, the crystalline forms and solid pharmaceutical formulations of the present invention may be administered before, during, or after surgical procedure and/or radiation therapy. The compounds of the invention can also be administered in conjunction with other anti-cancer drugs including those used in antisense and gene therapy.

A "subject" or "patient" is meant to describe a human or vertebrate animal including a dog, cat, marmoset, horse, cow, pig, sheep, goat, elephant, giraffe, chicken, lion, monkey, owl, rat, squirrel, slender loris, mouse, hamster, chinchilla, ferret, rat, guinea pig, gerbil, rabbit and sugar glider.

In one embodiment of the invention is a method of treating a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase which includes administering an effective amount of a solid pharmaceutical formulation containing a non-hydrate crystalline form of a lactic acid salt of the compound of formula I, such as the crystalline form which is Form A, to a patient in need thereof. Preferably, the formulation is a powder formulation, suitable for oral administration.

In one embodiment of the invention is a method for inhibiting tumor growth in a patient includes administering an effective amount of a solid pharmaceutical formulation containing a non-hydrate crystalline form of a lactic acid salt of the compound of formula I, such as the crystalline form which is Form A, to a patient having a tumor. Preferably, the formulation is a powder formulation, suitable for oral administration.

In one embodiment of the invention is a method for inhibiting the proliferation of capillaries in a patient which includes administering an effective amount of a solid pharmaceutical formulation containing a non-hydrate crystalline form of a lactic acid salt of the compound of formula I, such as the crystalline form which is Form A, according to a patient in need. Preferably, the formulation is a powder formulation, suitable for oral administration.

In one embodiment of the invention is a method of preparing solid pharmaceutical formulations which includes mixing a non-hydrate crystalline form of a lactic acid salt of the compound of formula I, such as the crystalline form which is Form A, with a

pharmaceutically acceptable carrier. Preferably, the formulation is a powder formulation, suitable for oral administration.

In further embodiments, the present invention provides a method of treating a patient with a solid formulation containing a non-hydrate crystalline form of a lactic acid salt of the compound of formula I, by oral administration of the formulation to the patient. In some embodiments, the non-hydrate crystalline form of a lactic acid salt of the compound of formula I is a mono-lactic acid salt. In some embodiments, the non-hydrate crystalline form of a lactic acid salt of the compound of formula I corresponds to Form A. In some embodiments, the solid formulation is in the form of a powder. In some embodiments, the solid formulation can be prepared by compaction or other treatment of a powder containing the non-hydrate crystalline form of a lactic acid salt of the compound of formula I. In further embodiments, the solid formulation of can be prepared in the form of a pill, tablet, capsule, or a caplet.

In some embodiments, the crystalline form of the lactic acid salt of the compound of formula I which is present in the solid formulation remains substantially a non-hydrate crystalline form, such as Form A, under ambient conditions for a period greater than about 36 hours, greater than about 1 week, greater than about 1 month, greater than about 6 months, or greater than about 1 year.

According to embodiments of methods of treating a patient, the patient can be a cancer patient. In some embodiments, the patient is diagnosed with multiple myeloma (MM), acute myelogenous leukemia (AML), prostate cancer, breast cancer, colon cancer, or melanoma. In further embodiments, the patient is a refractory patient, such as a patient showing resistance to preexisting therapeutics or treatment regimens, including prescribed/clinical dosing schedules. In some embodiments, the patient can be treated with a dose that is less than the maximum tolerated dose (MTD), such as a dose of about 0.25 to 30 mg/kg of the lactic acid salt of the compound of formula I. "MTD," as used herein, refers to the highest dose during diagnostic, prophylactic or therapeutic procedures that a body can tolerate without substantial injury. The MTD is reviewed in context of alteration of physiological function which would be predicted to alter a patients life span. Factors include: no more than 10% decrease in body weight gain relative to controls, target organ toxicity, and significant alterations in clinical pathological parameters.

In some embodiments, the solid formulations of the invention are solids at the time of administration to a patient which would include, for example, direct ingestion (e.g. via the mouth) of a pill, tablet, capsule, caplet or the like, as opposed to, for example, ingestion of a

solution or suspension made by mixing a solid formulation with liquid media prior to ingestion.

In further embodiments, each unit dose containing a solid formulation of the invention is sufficient to provide at least one of:

(a) a C_{max} of about 20 to 4000 ng/mL of the compound of Formula I in a subject's plasma or a C_{max} of about 40 to 8000 ng/mL of the compound in the subject's blood when it is administered to the subject;

(b) about 10 to 2,000 ng/mL of the compound in a subject's plasma 24 hours after administration or about 20 to 4,000 ng/mL of the compound in the subject's blood 24 hours after administration to the subject, or

(c) an AUC of about 500 to 60,000 ng*h/mL of the compound in a subject's plasma or about 750 to 120,000 ng*h/mL of the compound in the subject's blood when it is administered to the subject.

In further embodiments, each unit dose a solid formulation of the invention is sufficient to provide at least one of :

(a) a C_{max} of about 50 to 500 ng/mL of the compound in the subject's plasma or a C_{max} of about 100 to 1000 ng/mL of the compound in the subject's blood;

(b) about 20 to 1,000 ng/mL of the compound in the subject's plasma 24 hours after administration or about 40 to 2,000 ng/mL of the compound in the subject's blood 24 hours after administration; or

(c) an AUC of about 1,000 to 30,000 ng*h/mL of the compound in the subject's plasma or about 1,500 to 60,000 ng*h/mL of the compound in the subject's blood.

In further embodiments, each unit dose containing a solid formulation of the invention is sufficient to provide at least one of :

(a) a C_{max} of about 50 to 250 ng/mL of the compound in the subject's plasma or a C_{max} of about 100 to 500 ng/mL of the compound in the subject's blood;

(b) about 40 to 500 ng/mL of the compound in the subject's plasma 24 hours after administration or about 80 to 1,000 ng/mL of the compound in the subject's blood 24 hours after administration; or

(c) an AUC of about 2,000 to 15,000 ng*h/mL of the compound in the subject's plasma or about 3,000 to 30,000 ng*h/mL of the compound in the subject's blood.

In further embodiments, each unit dose containing a solid formulation of the invention is sufficient to provide at least one of :

(a) a C_{max} of about 75 to 150 ng/mL of the compound in the subject's plasma or a C_{max} of about 150 to 300 ng/mL of the compound in the subject's blood; or

(b) about 40 to 250 ng/mL of the compound in the subject's plasma 24 hours after administration or about 80 to 500 ng/mL of the compound in the subject's blood 24 hours after administration.

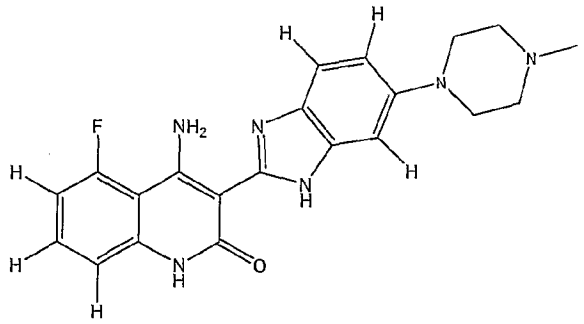
In further embodiments, each unit dose containing a solid formulation of the invention is sufficient to provide a C_{max} of about 100 to 2000 ng/mL of the compound in the subject's plasma or a C_{max} of about 200 to 4000 ng/mL of the compound in the subject's blood.

In further embodiments, each unit dose containing a formulation of the invention is sufficient to provide a C_{max} of 100 to 1000 ng/mL of the compound in the subject's plasma or a C_{max} of about 200 to 2000 ng/mL of the compound in the subject's blood

In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

Hydrates: Forms B, C, D, and E

In a second aspect, the present invention provides, *inter alia*, a crystalline hydrate of a lactic acid salt of a compound of Formula I:



I.

In some embodiments of the hydrates of the present invention, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I is about 1 or about 6.

In some embodiments, a hydrate of the present invention is a monohydrate or hexahydrate.

In some embodiments of the monohydrates of the present invention, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I is about 1.

In some embodiments of the hexahydrates of the present invention, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I is from about 4 to about 6.

In some embodiments of the hexahydrates of the present invention, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I is from about 5 to about 6.

In some embodiments of the hexahydrates of the present invention, the molar ratio of the hydrate water to the lactic acid salt of the compound of Formula I is about 6.

Hydrated lactic acid salts can further include mono- and di-acid salt forms, and the like. Preferably, the lactic acid salt is a mono-lactic acid salt of the compound of formula I. Di-lactic acid salts (i.e., bis-lactic acid salts), tri-lactic acid salts (i.e., tris-lactic acid salts) and intermediate and higher orders of salts are also encompassed and can be formed by the combination of greater than one equivalent of lactic acid with the compound of formula I according to routine methods of preparing acid addition salts. In some embodiments of the hydrates of the present invention, the lactic acid salt of the compound of Formula I is a mono-lactic acid salt.

In some embodiments, the crystalline hydrate form of the lactic acid salt of the compound of formula I is crystalline Form B, Form C, Form D or Form E.

Forms B, C, D and E can be characterized by any one or more solid state techniques such as X-ray powder diffraction (XRPD), single crystal X-ray diffraction, differential scanning calorimetry (DSC), dynamic vapor sorption (DVS), crystal morphology, solid state nuclear magnetic resonance, Raman scattering, infrared (IR) spectroscopy, thermogravimetry (TG), thermogravimetry (TG) coupled with Fourier-Transform Infrared (FTIR) spectroscopy (TG-FTIR) and the like. In some embodiments, forms B, C, D and E can be identified by their XRPD pattern. In some embodiments, forms B, C, D and E can be identified by its DSC thermogram. In some embodiments, forms B, C, D and E can be identified by crystal morphology. In some embodiments, forms B, C, D and E can be identified by its DVS cycle. Other techniques, alone or in combination with the ones recited herein, can also be used to identify forms B, C, D and E.

Form B

In some embodiments of the present invention, the crystalline hydrate form of the lactic acid salt of the compound of formula I is crystalline Form B. Crystalline Form B is characterized as a crystalline monohydrate of a lactic acid salt of the compound of formula I.

In some embodiments of Form B, the lactic acid salt is a mono-lactic acid salt. Form B can be identified by its X-ray powder diffraction (XRPD) pattern which is provided in Figure 6. In some embodiments, the crystalline Form B of the invention has an XRPD pattern substantially as shown in Figure 6 (two-theta values provided in Example 10), where the term "substantially" in this instance indicates that two-theta values for individual peaks can vary about ±0.2°. The relative intensities of the peaks can also vary, depending upon the sample preparation technique, the sample mounting procedure and the particular instrument employed. Powder X-ray diffraction two-theta data consistent with Form B is provided in Example 10 below. As discussed above, many factors can affect the 2-theta values. Therefore, the peak assignments listed in Example 10 can vary by plus or minus about 0.2°.

The crystalline Form B of the invention can be further recognized by its differential scanning calorimetry (DSC) thermogram which has a characteristic endotherm at about 155°C (peak maximum) with a $\Delta H \sim 100$ J/g.. In some embodiments, the crystalline Form B of the invention has a DSC trace substantially having the endotherm substantially as described above, it being understood that the term "substantially" in this instance indicates that features such as endotherms, exotherms, baseline shifts, etc. can vary about ± 4 °C. For DSC, it is known that the temperatures observed will depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms can vary by plus or minus about 4 °C.

TG-FTIR analysis of Form B samples revealed a weight loss of about 3.7%. At a heating rate of 10 K/min the weight loss started just above ambient temperature and the 3.7% of water were completely removed near 150°C. Further analysis of the water content by Karl Fischer titration (also determined to be about 3.7%) confirms that the weight loss in the TG-FTIR is essentially corresponding to the water content. Although not wishing to be bound by any particular theory, Form B is characterized as a monohydrate, since the theoretically expected water content of a monohydrate of the mono-lactic acid salt of the compound of formula I is 3.7%.

Crystalline Form B can be prepared by any of numerous methods in the art. In some embodiments, Form B can be prepared by suspending Form A in a solution which comprises water and an organic solvent at a temperature of about 20 °C to about 60 °C, wherein the organic solvent comprises an alcohol, a ketone, an organic nitrile, or mixture thereof, and

wherein the water is present in the solution in an amount of about 5% to about 20% by volume.

An example method for preparing Form B is as follows:

(a) suspending Form A in a solution which comprises water and an organic solvent at a temperature of about 20 °C to about 60 °C for a period of time sufficient to afford the Form B; and

(b) and isolating Form B.

Suitable organic solvents include those in which the newly-formed Form B is not readily soluble so that the Form B can be isolated. Example organic solvents include alcohols (e.g., methanol, ethanol, ispropanol, glycols, etc.), ketones (e.g., acetone, methylethyl ketone, etc.) and nitriles (e.g., acetonitrile, propionitril, etc.), mixtures thereof, and the like. In some embodiments, the organic solvent comprises one or more of ethanol, acetone, and methyl ethyl ketone. In some embodiments, the organic solvent contains an alcohol such as methanol or ethanol. In some embodiments, the organic solvent contains a ketone such as acetone or methylethyl ketone. In some embodiments, the organic solvent contains a nitrile such as acetonitrile.

The water content in the solution will typically be less than about 20% by volume. In some embodiments, the water is present in the solution in an amount of about 5% to about 20% by volume. In some embodiments, the water is present in the solution in an amount of about 5% to about 10% by volume. In some embodiments, the water is present in the solution in an amount of about 10% to about 20% by volume.

The suspending is carried out at any suitable temperature to afford Form B such as a temperature of about 20 °C to about 60 °C. In some embodiments, the suspending is carried out at a temperature of about 20 °C to about 30°C. In some embodiments, the suspending is carried out at a temperature of about 23 °C. In some embodiments, the suspending is carried out at a temperature of about 40 °C to about 60°C. In some embodiments, the suspending is carried out at a temperature of about 50 °C.

The suspending can be carried out for a period of time sufficient to afford Form B. In some embodiments, the suspending is carried out for about 20 hours to about 100 hours. In some embodiments, the suspending is carried out for about 20 hours. In some embodiments, the suspending is carried out for about 50 hours. In some embodiments, the suspending is carried out for about 100 hours.

In some embodiments, the water is present in the solution in an amount of about 10% by volume; the organic solvent comprises one or more of ethanol, acetone, and methyl ethyl

ketone; and the suspending is carried out at a temperature of about 20 °C to about 30 °C. In some embodiments, the water is present in the solution in an amount of about 5% by volume; the organic solvent comprises acetonitrile; and the suspending is carried out at a temperature of about 40 °C to about 60 °C.

The starting concentration of Form A in the solution can vary. It is postulated that the water in the solution is responsible for the formation of Form B (which is a hydrate). In some embodiments, the concentration of Form A in the solution is about 100 to about 140 or about 120 mg/mL.

It should be recognized that the Form A in the suspending step can be generated according to a variety of methods described herein. In some embodiments, the generation of Form A and suspending of Form A in the solution to afford Form B can be carried out in one process.

Form C

In some embodiments of the present invention, the crystalline hydrate form of the lactic acid salt of the compound of formula I is crystalline Form C. Crystalline Form C is characterized as a crystalline hydrate of a lactic acid salt of the compound of formula I, wherein the hydrate content lies between the mono- and the sesquihydrate. In some embodiments of Form C, the lactic acid salt is a mono-lactic acid salt.

Form C can be identified by its X-ray powder diffraction (XRPD) pattern as provided in Figure 7. Relatively prominent two-theta peaks were found at from about 3.2 to about 3.6, at from about 6.5 to about 7.1, at from about 9.8 to about 10.6, at from about 13.3 to about 14.1, at from about 17.6 to about 17.8, at about 18.8, at about 20.2, at from about 24.7 to about 24.9, at about 27.3 to about 27.5, at about 28.0, and at from about 29.0 to about 29.3°. In some embodiments, the crystalline Form C of the invention has an XRPD pattern substantially as shown in Figure 7 (two-theta values provided in Example 11), where the term "substantially" in this instance indicates that two-theta values for individual peaks can vary about ±0.2°. The relative intensities of the peaks can also vary, depending upon the sample preparation technique, the sample mounting procedure and the particular instrument employed. Powder X-ray diffraction two-theta data consistent with Form C is provided in Example 11 below. As discussed above, many factors can affect the 2-theta values. Therefore, the peak assignments listed in Example 11 can vary by plus or minus about 0.2°.

The XRPD patterns of Form C as provided in Figure 7 can vary slightly, suggesting that Form C can adsorb variable amounts of water. A higher water content is likely to lead to

a slight lattice expansion (larger d-spacings) with a concurrent shift of the XRPD peaks to smaller angles.

Crystalline Form C of the invention can be further recognized by its differential scanning calorimetry (DSC) thermogram which shows a very small exothermic signal between about 50 °C and about 80 °C which is attributed to crystallization of a small amount of residual amorphous form. Between about 80 and about 140 °C several small endothermic signals (at about 109 °C, 115 °C and 127 °C) and one small exothermic signal (at about 121 °C) suggest that multiple phase transitions are taking place. These effects are followed by a strong endothermic signal (ΔH = 35 J/g) with a peak near about 150 °C. In some embodiments, the crystalline Form C of the invention has a DSC trace having substantially the values described above, where the term "substantially" in this instance indicates that features such as endotherms, exotherms, baseline shifts, etc. can vary about ± 4 °C. For DSC, it is known that the temperatures observed will depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms can vary by plus or minus about 4 °C.

TG-FTIR analysis of Form C samples revealed a weight loss of about 4.6%, which corresponds to an amount that lies between the mono- and the sesquihydrate.

Investigation of Form C in a DVS experiment, such as provided in Example 11, reveals a water content of about 6.5% at the start of the measurement and about 4.8% at the end of the measurement. However, the Raman spectrum of the recovered sample corresponds substantially to Form C. Although not wishing to be bound by any particular theory, the reason for the irreversibility found for Form C is believed to be due to some remaining amorphous material that is crystallizing during the measurement. Then the water content of Form C would indeed be about 4.6%, as found for the sample used in the DSC experiment as shown herein. This amount of water would correspond to 4/3 water molecules per formula unit (i.e., sesquihydrate).

Crystalline Form C can be prepared by any of numerous methods in the art. In some embodiments, Form C can be prepared by diffusing organic solvent vapor into an aqueous solution of the lactic acid salt of the compound of Formula I at a temperature of about 0 °C to about 10 °C. In some embodiments, Form C can be prepared by contacting the amorphous form of the lactic acid salt of the compound of Formula I with a relative humidity of from about 50% to about 75% at a temperature of from about 40 °C to about 80 °C.

An example method for preparing Form C is as follows:

(a) diffusing organic solvent vapor into an aqueous solution of said lactic acid salt of said compound of Formula I at a temperature of about 0 °C to about 10 °C for a period of time sufficient to afford the Form C; and

(b) and isolating Form C.

Suitable organic solvents include those in which the newly-formed Form C is not readily soluble so that the Form C can be isolated. Example organic solvents include alcohols (e.g., methanol, ethanol, ispropanol, glycols, etc.), ketones (e.g., acetone, methylethyl ketone, etc.) and nitriles (e.g., acetonitrile, propionitril, etc.), mixtures thereof and the like. In some embodiments, the org

acetonitrile.

In some embodiments, more organic